

**REMARKS**

**I. Examiner Interview**

Applicants thank the Examiner for her time and consideration in the telephone interview between the Examiner and Applicant's representative on November 29, 2010.

During the interview, Applicant's representative noted that Applicants would like to amend the claims to recite the subject matter indicated as enabled in the outstanding Office Action. However, Applicants were concerned because the Office Action seemed to suggest that a control level of gene expression must be determined, for comparative purposes, each time the gene expression is assayed in a test sample. Applicants' representative pointed out that the method would not be practical for clinical use if each time a blood sample from a cancer patient is tested the assay would also need to be carried out with a control sample from a healthy patient. Instead, the control levels of gene expression can be pre-determined. The Examiner agreed that the steps for determining a control level of gene expression could be recited in a "wherein" clause to clarify that the control need not be determined each time the assay is carried out on a test sample.

**II. Claim Amendments and Response to Claim Rejections Under 35 U.S.C. § 112, First Paragraph**

Not to acquiesce to the rejection, but to advance prosecution, the present claims have been amended to recite, at least in part, the subject matter indicated as allowable (enabled) in the outstanding Office Action. In particular, independent claim 26 has been amended to more precisely define the method steps; dependent claims 32, 34, and 46 have been amended to properly depend from amended claim 26; and claims 27-31, 33, 35-45, and 47-70 have been canceled. Claims 71-73 have been added. The amendments to the claims are supported throughout the application as filed.

The amendments to the claims, including cancellation of claims, have been made without prejudice or disclaimer to any subject matter recited or canceled herein. Applicants reserve the right to file one or more continuation and/or divisional applications directed to any canceled subject matter. No new matter has been added, and entry of the foregoing amendments to the claims is respectfully requested.

With regard to the subject matter that differs from the subject matter specifically indicated as allowable in the outstanding Office Action, Applicants provide the following comments:

Step (a) of claim 26 has been amended to recite "Collecting a cell fraction that comprises mononuclear cells (MNC fraction)" instead of "collecting mononuclear cells from the blood sample," as recommended by the Examiner. Given that said fraction may contain other cells than MNCs (e.g. cancer cells), Applicants respectfully submit that this wording better reflects the actual teaching of the invention.

In addition, step (a) of claim 26 recites "screen with a defined mesh or pore width" instead of "screen with a defined mesh;" and "17-27  $\mu\text{m}$ " instead of "20  $\mu\text{m}$ ." Applicants note that a mesh or pore width of 20  $\mu\text{m}$  would be too easy to design around. The Examiner's attention is drawn to U.S. Patent No. 7,232,653 (Applicant's patent to the screening method). Claim 1 of US 7,232,653 relates to a method using a screen which has a mesh or pore width of about 15 to 30  $\mu\text{m}$  and the claimed method was acknowledged to yield the large M1 tumor cells. Thus, a person of ordinary skill in the art would recognize that screens having a mesh or pore width of about 15 to 30  $\mu\text{m}$  (including the range 17-27  $\mu\text{m}$ ) yield cancer cell fractions which are similar to the fraction obtained with the 20  $\mu\text{m}$  screen.

Step (c) of claim 26 recites "mRNA encoding protein with defined amino acid sequence" instead of "using defined primers." A method using specific primers is too easy to design around. The claims now clearly define the marker genes by reference to the expressed protein. Designing appropriate primers is a matter of routine. Applicants further note that new dependent claim 71 recites exactly the mRNAs whose cDNAs are amplified in the working examples.

Step (e) of claim 26 recites "comparing with a control limit for expression in blood samples of healthy human subjects" instead of "the sequence of steps (f) to (g)." Given that steps (a) to (d) are defined in the claim, it would be a matter of routine for the person of average skill in the art to determine an appropriate control limit of expression in blood samples of healthy human subjects. The claim requires that there is a control limit to be compared with, but Applicants respectfully submit that the claim does not need to state how the limit is determined.

New dependent claims 72 and 73 depend from claim 71 and recite essentially the steps for determining the control limit recommended by the Examiner. Applicants note that step (g) of

claim 72 is optional, because in step (h) not only fraction A but alternatively fraction A' can serve as a reference fraction. Applicants further note that both test fraction A' and reference fraction A' can provide an expression value for a blood cell fraction that has not been subjected to a method of isolating cancer cells. As fraction A' is used as a test fraction it can also be used as a reference fraction. With regard to step (h) of claim 72, a person of ordinary skill in the art would probably not determine the limit as the average plus one standard deviation but rather apply other statistical methods to evaluate whether the expression in the test fraction is significantly higher (compare, for instance, Giesing et al., 2009). Furthermore, statistics were matter of routine at the time of filing.

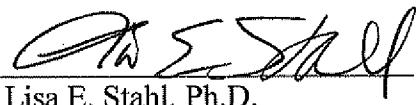
Applicants submit that the claims as amended are fully enabled by the application as filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

**CONCLUSION**

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions related to this response, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney at the below-listed telephone number concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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